PC 10384 A
RC/P

[51] Int. Cl.[2]: C 07 C 143 -78

[19] FEDERAL REPUBLIC OF GERMANY

[emblem]

GERMAN PATENT OFFICE

[11] *OFFENLEGUNGSSCHRIFT* 24 44 720

[Unexamined Patent Application]

[21] File No.: P 24 44 720.9

[22] Filing date: September 19, 1974

[43] Disclosure date: April 10, 1975

[30] Union priority:

[32] [33] [31] October 2, 1973 France 7335277

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[54] Title: Process for the preparation of 2 -alkoxy -5 -substituted sulfamoyl benzoic acids

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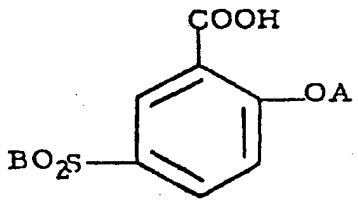
Process for the preparation of 2 -alkoxy -5 -substituted sulfamoyl benzoic acids.

The invention relates to a process for the preparation of 2 -alkoxy -5 -substituted sulfamoyl benzoic acids having the general formula (VI)



In the general formula A denotes an alkyl or alkenyl group of low molecular weight with 1 to 5 carbon atoms and B denotes an amino or monoalkylamino group of low molecular weight or a dialkylamino group of low molecular weight, in which the alkyl groups can be connected to each other, with formation of a ring containing optionally nitrogen, oxygen or sulfur.

When the ring contains a nitrogen atom, the nitrogen atom can be linked with an alkyl group of low molecular weight.

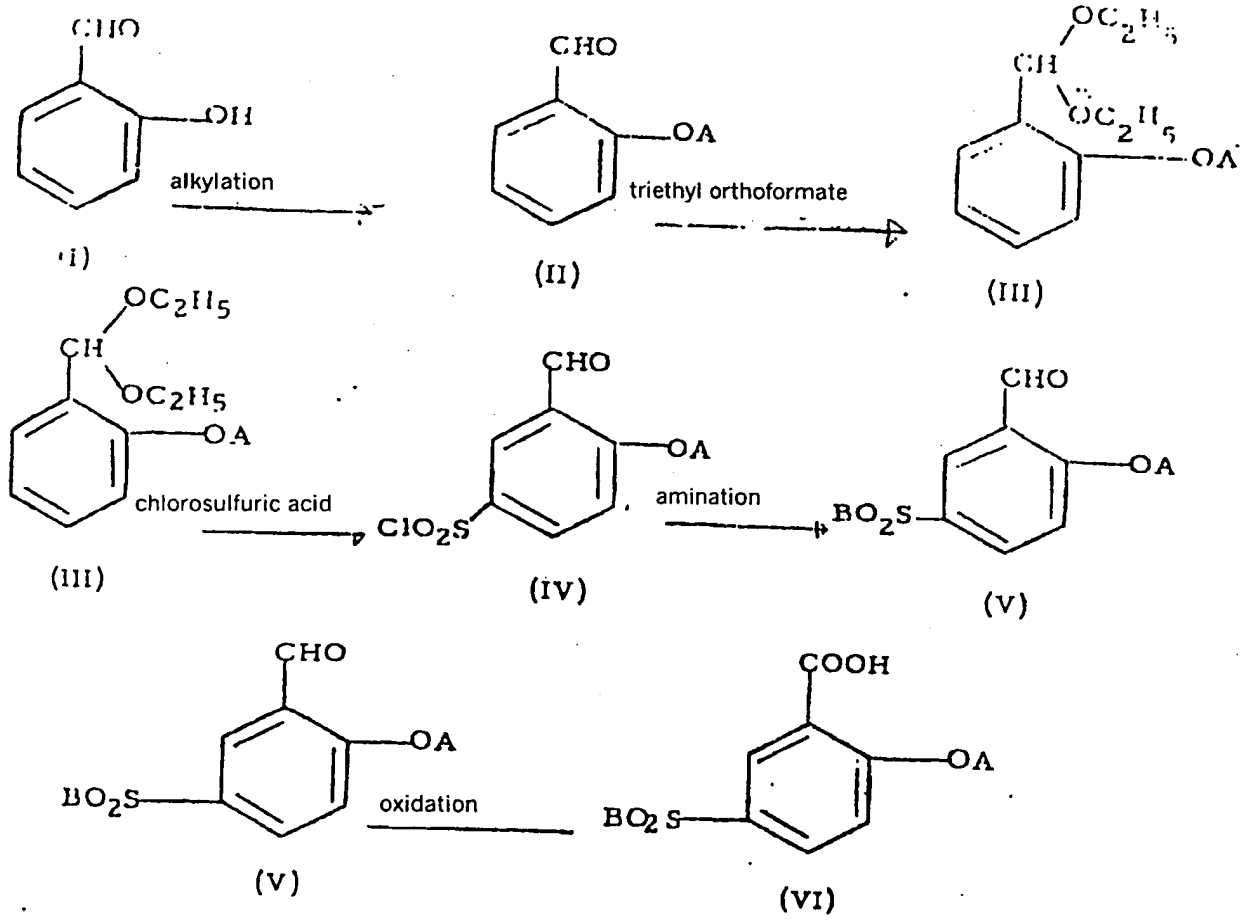
The rings thus formed can be, for example, pyrrolidinyl, piperidinyl, imidazolidinyl, piperazino, morpholino or thiazolidinyl groups.

The process according to the invention relates to the treatment of salicylaldehyde (I) with an alkylating agent with formation of 2 -alkoxy -5 -benzaldehyde (II), which is reacted with triethyl orthoformate to obtain 2 -alkoxybenzaldehyde diethyl acetal (III). The compound (III) is a novel product when A is an alkyl group containing 2 to 5 carbon atoms. This acetal, when treated with clorosulfuric acid, yields the corresponding 2 -alkoxy -5 -chlorosulfonylbenzaldehyde (IV), which is a novel product.

Treatment with ammonia or an amine yields the desired 2 -alkoxy -5 -substituted sulfamoyl benzaldehyde (V), which, with the exception of 2 -alkoxy -5 -sulfamidobenzaldehyde, is a novel product that is then oxidized by means of an oxidation agent, with formation of the corresponding 2 -alkoxy -5 -substituted sulfamoyl benzoic acid.

The invention further relates to the novel intermediate products required for the processes according to the invention, i.e., 2 -alkoxybenzaldehye diethyl acetal, excepting 2 -methoxybenzaldehyde diethyl acetal, 2 -alkoxy -5 -chlorosulfonylbenzaldehyde and 2 -alkoxy -5 -subst. sulfamoylbenzaldehyde, with the exception of 2 -alkoxy -5 -sulfamidobenzaldehyde.

The following diagram illustrates the reaction sequence of the processes according to the invention:



The agent used for the alkylation of the phenol function is either an alkyl halide, e.g., ethyl bromide* or the like, or an alkyl sulfate, e.g., dimethyl sulfate, diethyl sulfate or a substituted or unsubstituted alkylaryl sulfonate, e.g., methylbenzene sulfonate or butyl -p -toluene sulfonate.

The amination agent used for converting the sulfochloride group to the sulfamido group can be ammonia, ammonium carbonate or an amine, e.g., dimethylamine, piperidine, morpholine or the like. It is also possible to use salts of such amines when it has been assured that the free amine was first released from its salt by means of an alkaline reagent.

The oxidation agent used according to the invention may be, for example, potassium permanganate or potassium dichromate.

The 2 -alkoxy -5 -substituted sulfamoyl benzoic acids prepared according to the invention are valuable synthetic intermediate products for the preparation of 2 -alkoxy -5 -sulfamoyl benzamides, which possess important pharmacological properties, for example as antiemetics, neuroleptics, local anesthetics and the like. Especially beneficial products along these lines are, for example, N -(diethylaminoethyl) -2 -methoxy -5 -sulfamidobenzamide and N –(1 -ethyl -2 -pyrrolidinylmethyl) -2 -methoxy -5 -sulfamidobenzamide.

The invention is illustrated in greater detail below on the basis of an example of an embodiment that should not, however, be understood as restrictive.

Example:

2 -methoxy -5 -sulfamidobenzoic acid

Step I: 2 -methoxybenzaldehyde

Introduce 122 g (1 mol) salicylaldehyde and 550 mL 2N sodium hydroxide into a 2 -liter round -bottomed flask equipped with a stirrer, a thermometer, a reflux condenser and a dropping funnel. Stir this mixture for 30 minutes and add 95 mL dimethyl sulfate drop by drop. The temperature increases to 40 -45° C. Then stir the entire batch for 5 minutes and add 275 mL of 2N sodium hydroxide. Another 47.5 mL dimethyl sulfate is poured in. Maintain the temperature at 45 -50° C. Stir the mixture for 30 minutes at this temperature and then cool it. It is then extracted three times with 400 mL ether and the organic extract is dried over magnesium sulfate, filtered and concentrated by evaporation. The residue is distilled in vacuo.

The quantity obtained is 100 g (yield: 74%) of 2 -methoxybenzaldehyde (boiling point/5 mm: 95 –96° C).

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* propyl iodide

Step II: 2 -methoxybenzaldehyde diethyl acetal

Introduce 96 g (0.70 mol) 2 -methoxybenzaldehyde, 114 g (0.77 mol) triethyl orthoformate, 98 g ethanol and 1.5 g ammonium chloride into a 1 -liter round -bottomed flask equipped with a stirrer and a reflux condenser.

Slowly heat the mixture to reflux and then let stand under these conditions for 1.5 hours for the purpose of the reaction. Then cool, evaporate the alcohol in vacuo, filter the ammonium chloride and distill the product in vacuo.

The quantity obtained is 120 g (yield: 82%) of 2 -methoxybenzaldehyde diethyl acetal (boiling point/2 mm: 102° C).

Step III: 2 -methoxy -5 -chlorosulfonylbenzaldehyde

Introduce 2030 g (17.4 mol) chlorosulfuric acid into a 2 -liter round -bottomed flask equipped with a stirrer and a reflux condenser, and cool it to about –5° C. Then add 80 g (0.38 mol) of 2 -methoxybenzaldehyde diethyl acetal drop by drop over a period of 1 1/4 hours without letting the temperature increase to above 0° C. Then allow the mixture to stand for 3 hours while stirring, during which the temperature may increase, but not over 15° C. After this allow the mixture to stand overnight in a condenser or refrigerator. Then carefully pour the solution, while vigorously stirring it, over ground ice. Filter the solution, wash the product with ice water and dry it over phosphoric anhydride in a desiccator in vacuo.

The quantity obtained is 69 g (yield: 78%) of 2 -methoxy -5 -chlorosulfonylbenzaldehyde (melting point: 85° C).

Step IV: 2 -methoxy -5 -sulfamidobenzaldehyde

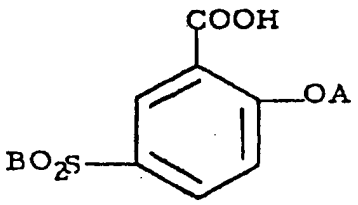
Introduce 29 g (0.123 mol) 2 -methoxy -5 -chlorosulfonylbenzaldehyde and 500 mL chloroform in a 1 -liter round -bottomed flask equipped with a stirrer, a gas -inlet device and a reflux condenser.

Stir the mixture to cause the components to dissolve. Then pass a stream of ammonia into the solution until a precipitate no longer forms. Then decant the chloroform, evaporate the solvent and combine the residue with the precipitate previously obtained. Suspend the solid in 400 mL of water. Then add 130 mL of 50% hydrochloric acid. Heat the suspension under reflux, then subject the insoluble material to filtration under heat and allow the product to crystallize in a condenser or refrigerator. Filter the product, wash it with water and dry it in a desiccator in vacuo.

The quantity obtained is 21 g (yield: 80%) of 2 -methoxy -5 -sulfamidobenzaldehyde (melting point: 112° C).

Patent claim

Process for the preparation of 2 -alkoxy -5 -substituted sulfamoyl benzoic acids having the general formula



in which A denotes an alkyl or alkenyl group of low molecular weight with 1 to 5 carbon atoms and B denotes an amino or monoalkylamino group of low molecular weight or a dialkylamino group of low molecular weight, in which the alkyl groups can be connected to each other, with formation of a ring containing optionally nitrogen, oxygen or sulfur, where, in the case of a ring containing a nitrogen atom, the said ring can be linked with an alkyl group of low molecular weight and where the rings formed can be, e.g., pyrrolidinyl, piperidinyl, imidazolidinyl, piperazino, morpholino or thiazolidinyl groups, **characterized by** treating salicylaldehyde as starting material with an alkylating agent, converting the 2 -alkoxybenzaldehyde obtained with triethyl orthoformate, treating the 2 -alkoxybenzaldehyde diethyl acetal obtained with chlorosulfuric acid, converting the 2 -alkoxy -5 -chlorosulfonylbenzaldehyde obtained with ammonia or an amide, and oxidizing the desired 2 -alkoxy -5 -substituted sulfamoylbenzaldehyde with an oxidizing agent.